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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Nicholas J. Seay
Quarles & Brady LLP
P O Box 2113
Madison, WI 53701-2113

EXAMINER	
MARVICH, MARIA	
ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/774,122	ZWAKA ET AL.	
	Examiner	Art Unit	
	MARIA B. MARVICH	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-21* is/are pending in the application.

4a) Of the above claim(s) *5,6,11 and 14-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,7-10,12, 13, 17 and 18-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/13/09 has been entered. Claims 1 and 3-21 are pending. Claims 5, 6, 11 and 14-16 are withdrawn. Therefore, claims 1, 3, 4, 7-10, 12, 13, 17 and 18-21 are under examination in this action.

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Claim Objections

Claims 1, 3, 4, 7, 8 and 12 are objected to because of the following informalities: claims 1 and 7 are drawn to a genetic construct which is a targeting vector comprising an insert flanked by 5' and 3' arms wherein the construct includes a marker gene for cellular identification. However, the marker gene must be flanked by the 5' and 3' arms as the method requires recombination with a genomic region such that the insert and marker are inserted into the genome. The marker cannot be in any location except between the 5' and 3' flanking arms. It would be remedial to amend line 4 to recite --an insert and a marker gene-- and in line 10-11, --identifying cells which express the marker gene and hence the insert--.

Claims 1, 7 and 17 are drawn to electroporation of clumps of stem cells. However, the reception in lines 7 "selected regions of the stem cell genome" has not been amended to reflect that there are multiple genomes and not only one.

Claim 3 intends on insertion of the construct into the genome such that a genomic promoter that functions in specific states of differentiation is operably linked to the marker gene. However, the claim lacks a number of details that will provide clarity to the claim. For example, --the construct is designed such that upon recombination with the selected regions, the marker gene is operably linkage with a differentiation specific promoter wherein the marker gene is expressed only in cells in a desired state of differentiation--.

In claim 4, "being active" should be amended to --active-- for grammatical purposes. Similarly in claim 8, the phrase "a promoter is active to express a gene only" should be amended to --a promoter which is specifically active--.

Claim 8 repeats several steps from claim 7 which confuses the purpose of claim 12. Claim 7 is already directed towards methods of purifying cells of a defined lineage. It would be clearer to recite --The method of claim 7 further comprising a) identifying expressed genes characteristic of the cells of the defined lineage--

Appropriate correction is required.

Claim 13 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 12 recites that the cells of a defined lineage are purified following their differentiation. Claim 13 improperly recites that these cells are undifferentiated. Hence, this is a specie of cells that is not encompassed by the species recited in claim 12.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4, 7, 8, 10, 12, 17 and 18-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al (US 6,146,888; see entire document) in view of Jaynes et al (US 6,303,568; see entire document) or Chalitta-Eid (US 7,135,549; see entire document) as evidenced by Tenner et al (US 5,965,439; see entire document) or Tajima et al (PNAS, 1998, ; see entire document) further in view of Prasad et al (In Vitro Cell Dev Biol Anim. 1994 May;30A(5):321-8) and Takada et al (Cell Transplant. 2002;11(7):631-5). **This is a new rejection necessitated by applicants' amendment.**

Applicants claim a method of introducing a targeting vector comprising a marker gene into clumps of hES cell by electroporation in culture medium for homologous recombination.

Smith et al teach use of a targeting construct to be used in homologous recombination wherein the construct is introduced into the cell by transfection. Contemplated cells are human embryonic stem cells. The vector is shown in figure 3 and comprises 5' and 3' flanking arms for homologous recombination as well as a marker to be selectively targeted to human ES cells (see e.g. bridging ¶, Col 1-2). The marker comprises a promoter that is selectively active in specific cell types (see e.g. claim 11). By transforming the cell with the marker construct and allowing

homologous recombination to occur, cells can be purified that selectively express the marker such as by FACS (see e.g. col 3, line 60-65).

However, Smith does not explicitly teach the steps of electroporation. Hence, the step of electroporation of clumps of cells in culture media wherein the method requires 320V and 200 microfarad is not explicitly stated.

However, the art teaches that hES cells are cultured as clumps (see Thomson et al, reference 16). Furthermore, methods of electroporation of cells at the time of filing required use of cell clumps (see Prasad et al). Hence, use of clusters of cells is not an advancement in the art. Hence, the question is does use of culture media in the electroporation method of the instant claims advance the state of the art. Jaynes et al teaches that electroporation is used to introduce DNA into a cell and is performed in culture medium (bridging ¶ col 6-7). In fact, Jaynes et al teaches use of this method for transfection of animal embryonic cells (see e.g. col 5, line 45-55). Challita-Eid teaches electroporation of ES cells using electroporation in culture medium. Furthermore, the method uses targeting vector with homologous arms (see e.g. col 35, line 1-35), which as evidenced by Tenner et al requires culture medium (see col 23-24, bridging ¶). Finally as regards claims 19-21, Tajima et al teaches electroporation using a single pulse of 320 V and 250 microfarads (page 11904, col 1, ¶ 4).

In KSR International Co. v. Teleflex lnc., 82 USPQ2d 1385 (U.S. 2007), the Supreme Court particularly emphasized "the need for caution in granting a patent based on a combination of elements found in the prior art," (Id. At 1395) and discussed circumstances in which a patent might be determined to be obvious. Importantly, the Supreme Court reaffirmed principles based

on it precedent that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." (Id. At 1395.)
In the instant case, Smith et al teach use of electroporation but do not provide the details to do so. Smith et al is directed to introduction of targeting vectors into embryonic stem cells wherein the vector is transfected into the cell by methods that include electroporation. At the time of the invention, electroporation was a well known method that was performed by application of electrical currents to cells wherein the cells were in culture medium. Without the culture medium, the cell would have not survived the electrical current. PBS has never been shown to be a superior method of electroporation. Furthermore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use culture medium in the method of electroporation taught by Smtih et al because Smith et al teach that it is within the ordinary skill of the art to use electroporation to introduce DNA into cells and because Jaynes et al and Challita-Eid in view of Tenner et al teach that it is part of the method to use culture medium. Tajima et al teaches that it was known to use a single pulse at 320V and 250 mF. One would have been motivated to do so in order to receive the expected benefit of protection of the cells during transformation. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Furthermore, the MPEP teaches, "When the prior art discloses a range which touches or overlaps the claimed range, but no specific examples falling within the claimed range are disclosed, a case by case determination must be made as to anticipation. In order to anticipate the claims, the claimed subject matter must be disclosed in the reference with “sufficient specificity

to constitute an anticipation under the statute." In fact, the MPEP 2144.05 teaches, "a prima facie case of obviousness exists where the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same properties. Titanium Metals Corp. of America v. Banner, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985)." Furthermore, the MPEP teaches that optimization of ranges through prior art conditions or through routine experimentation is "The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages." (MPEP 2144.05II). In this case use of clusters of cells in culture media is taught by the art.

The MPEP (2145) also teaches that "The Hoeksema court further noted that once a prima facie case of obviousness is made by the PTO through citation of references, the burden is on the applicant to produce contrary evidence establishing that the reference being relied on would not enable a skilled artisan to produce the different compounds claimed. Id. at 274-75, 158 USPQ at 601. See also Ashland Oil, Inc. v. Delta Resins & Refractories, Inc., 776 F.2d 281, 295, 297, 227 USPQ 657, 666, 667 (Fed. Cir. 1985) (citing Hoeksema for the proposition above); In re Grose, 592 F.2d 1161, 1168, 201 USPQ 57, 63-64 (CCPA 1979) ("One of the assumptions underlying a prima facie obviousness rejection based upon a structural relationship between compounds, such as adjacent homologs, is that a method disclosed for producing one would provide those skilled in the art with a method for producing the other... Failure of the prior art to disclose or render obvious a method for making any composition of matter, whether a compound or a mixture of compounds like a zeolite, precludes a conclusion that the composition would have been obvious."). In this case, the methods provide details omitted in the teachings of Smith

et wherein Tajima et al teach a method of electroporation wherein the conditions are similar and the differences do not appear to significantly alter the final method. Since, the methods are merely variants of one another, one would not conclude that the instant vector requires an inventive step over the prior art.

Claims 3, 9, 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al (US 6,146,888; see entire document) in view of Jaynes et al (US 6,303,568; see entire document) or Chalitta-Eid (US 7,135,549; see entire document) as evidenced by Tenner et al (US 5,965,439; see entire document) as applied to claims 1, 4, 7, 8, 10, 12, 17 and 18 above, and further in view of West et al (US 2004/0219563; see entire document). **This is a new rejection necessitated by applicants' amendment.**

Applicants claim a method of introducing a targeting vector comprising a marker gene into a cell by electroporation for homologous recombination wherein the vector does not comprise a promoter and wherein the cells are further differentiated following selection.

The teachings of Smith et al in view of Chalitta-Eid or Tenner are as above except the references do not teach that the construct is promoterless or that the cells are differentiated following transformation.

In ¶0180, West et al state that DNA markers can be inserted into human genes by homologous recombination. The markers are either inserted into sites so that they are transcriptionally regulated by the promoters of the genes into which they are inserted (see e.g. ¶0131) or comprise exogenous promoters that are development stage specific

promoter/regulatory elements (see ¶0199). In these methods it is preferable to use homologous recombination for insertion of the construct comprising a marker into a specifically selected site in a gene that is conditionally expressed in a differentiating cell to disrupt and inhibit expression of the endogenous gene to produce a knockout or inserted to be transcribed ¶0073. The method of West et al allows for isolation of cells in distinct differentiated states such that the gene profile can be determined (see e.g. ¶0199).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use targeting vectors lacking promoters as taught by West et al in the methods of homologous recombination as taught by Smith et al because West et al teach insertion of a promoterless marker into the genome in a sight that is regulated by the stage of differentiation and Smith et al teach that it is within the ordinary skill of the art to transform a hES by electroporation with markers to identify transformed cells. Methods of inserting heterologous sequences into sequences comprising endogenous regulatory sequences were well known in the art and one would have been motivated to insert a promoterless marker into the genome in order to receive the expected benefit of using regulatory sequences known to work in the transformed cell. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Argument

Applicants' arguments filed 7/13/09 have been fully considered but they are not persuasive. As to the lack of knowledge of human ES culture media at the time of filing of Smith

et al, the question is whether *at the time of filing* a person could have combined the teachings of Smith et al with what was known in the art could a person of skill in the art have performed electroporation of clumps of hES cells in culture media. As set forth above, the use of clumps of cells for electroporation as well as the use of clumps of hES cells for culturing was known in the art. The media used in the instant methods is standard ES cell culture medium and therefore are demonstrated to be an issue as set forth in the instant specification. Applicants have argued that the provided references do not teach use of clumps of cells or use of culture media. However, these are limitations that appear to be known but omitted from the references. Rather, as demonstrated by a review of the art, it was known to culture and electroporate clumps of cells. As well use of culture media appears to have been known and used with success. Electroporation of hES cells was not known to be highly successful at the time of filing. Which is supported by the instant specification, "[00026] Prior to using electroporation, we did explore the use of chemical agents to mediate transfection of human ES cells. Those efforts did not yield satisfactory results. We also used electroporation protocols for typical mouse ES cells, such as electroporation at 220 V, 960 mF, with an electroporation medium of phosphate buffered saline, PBS, but the results were a stable transfection rate of less than 10-7." The statement is also supported by Benvensity et al which also states that electroporation was reporter but the effort reflected in the instant specification was to improve the efficiency. However, applicants claims are broadly to electroporation of human ES cells wherein the method requires use of clumps of cells, which was known to be the method of culturing as well as was known to be useful in general electroporation methods, using culture media, which was also shown to be successfully used in methods of electroporation. Hence, the references provide limitations known that have

been used with predictable success which when combined perform the same function as they did separately. Absent an indication that there are secondary considerations, applicants have not demonstrated that the invention using commonly known techniques and methods of the art would have performed with success.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARIA B. MARVICH whose telephone number is (571)272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Maria B Marvich, PhD
Primary Examiner
Art Unit 1633

/Maria B Marvich/
Primary Examiner, Art Unit 1633